

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202293Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	January 8, 2014
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	202293
Applicant Name	Bristol-Myers Squibb
Proprietary / Established (USAN) Names	Farxiga Dapagliflozin
Dosage Forms / Strength	5- and 10-mg tablets
Proposed Indication(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Action:	<i>Approval</i>

1. Introduction and Discussion

This second cycle review will be a brief summary of the basis for the regulatory action regarding dapagliflozin and the reader should review the action package and my first cycle review for more detail. Dapagliflozin is a new molecular entity anti-diabetic therapy that inhibits the sodium glucose cotransporter-2 (SGLT2) receptor. Inhibition of this receptor is the proposed mechanism for treating hyperglycemia associated with diabetes as it prevents glucose reabsorption in the proximal tubules of the kidney resulting in glucosuria. Control of hyperglycemia through glucose diuresis results in excess caloric loss and may have other salutary effects, such as reducing blood pressure and weight loss. Regarding possible salutary blood pressure changes, it is unknown whether a glucose-induced 'diuretic' effect would provide the same beneficial cardiovascular outcome as traditional diuretic medications that exert their effects mainly through sodium balance.

During the first cycle of review, it was determined that dapagliflozin demonstrated efficacy in improving glycemic control in adults (with normal or mildly impaired renal function) with type 2 diabetes mellitus (T2DM). However, concerns arose regarding cardiovascular (CV) safety and a numeric imbalance in bladder cancer and a single case of potential dapagliflozin-induced liver injury. Dapagliflozin was the subject of an Advisory Committee (AC) meeting (July 19, 2011) during the first review cycle with the AC panel voting 6-yes and 9-no regarding approval. Many on the panel were concerned about potential safety issues of cancer and drug-induced liver injury (DILI) and felt further data were necessary.¹ After consideration of all available data and the comments from the AC meeting, a Complete Response (CR) action was taken with the request for further data.

¹ Potential cardiovascular concerns arose after the sponsor submitted further data, after the AC meeting. Therefore these concerns were not discussed at the first AC meeting.

In response to the CR action, the sponsor submitted a request for formal dispute resolution request (FDRR) on July 17, 2012. In essence, the sponsor requested that the Agency approve dapagliflozin with the available data. The FDRR was denied by the Agency agreeing that the path forward as written in the CR letter was reasonable and that when the specified data requested was resubmitted, the NDA should be brought before an advisory committee.

With this resubmission, the sponsor has included additional nonclinical and clinical data in an effort to remediate deficiencies identified in the first review period. This resubmission was also the subject of another AC meeting with the panel voting 13-yes and 1-no regarding approval.

Upon review of the data submitted in response to the first review cycle action as I will discuss further below, I believe that the sponsor has successfully addressed the identified concerns. I therefore recommend approval of this application.

Efficacy

Please refer to my first cycle review for efficacy considerations.

Safety

During the first cycle review, there were three main concerns that were identified including a possible drug-induced liver injury (DILI) highlighted by a case fulfilling Hy's Law and cancer signals for breast and bladder cancer and inconsistencies in cardiovascular (CV) evaluation between original data and interim data from two large trials, D1690C00018 and D1690C00019, henceforth referred to as Trial 18 and 19.

Hepatotoxicity

During the first cycle review, it was noted that there were not any pre-clinical animal signals of hepatotoxicity with dapagliflozin and there also is not any evidence of transaminitis 'shifts' that may indicate that there could potentially be concerns regarding DILI.

However, based on the data available at the time, there was a case potentially fulfilling Hy's Law criteria. Therefore a concern regarding DILI arose that could not be refuted with data available at the time of the first action. Further data contained within this resubmission now indicates that this case was likely due to autoimmune hepatitis. Therefore, we now do not have any indication that dapagliflozin is likely to be associated with DILI at a higher rate than the comparators within this database.

Cancer

Preclinical studies submitted in the original application determined that dapagliflozin was neither genotoxic nor clastogenic and animal carcinogenicity studies were negative at doses experienced in human study with adequate safety margins. However, during the clinical

review numerical imbalances were noted for bladder cancer (in men only) and breast cancer (in women) for subjects taking dapagliflozin.

Bladder Cancer

The original database had nine cases of bladder cancer in the dapagliflozin group versus one in the comparator, all in male subjects with a rate ratio of 4.0 (95% CI, 0.5-31.4). With an updated exposure database during the first review cycle, there were not any new cases of bladder cancer, but there was a greater percentage of comparator exposure such that the updated rate ratio increased to 5.4 (95% CI, 0.84-122.2). Exposure times for those cases of bladder cancer ranged from 43 days to 727 days. Since use of dapagliflozin is associated with increased urinary tract infections, an extensive evaluation of potential detection bias accounting for the imbalance was undertaken. Neither the review team nor the sponsor were able to discover any type of detection bias that may have accounted for increased surveillance in the dapagliflozin group compared to the control group.

This submission includes 40% more patient-years of exposure since the original submission and one new case of bladder cancer in a 53 year-old female subject treated with dapagliflozin. The all-gender estimated incidence risk ratio (IRR) is now 6.11 (95% CI, 0.827 to 272).²

Regarding preclinical evaluation, to supplement the original application the applicant submitted several studies intended to address tumor promoter potential. These studies included in vitro stimulation of tumor cell proliferation of six human bladder transitional cell carcinoma (TCC) cell lines, exposures in nude mice bearing human TCC tumors and human TCC cell lines exposed to increasing concentrations of glucose. None of these studies demonstrated a risk; however, they did not fully address the question as the human bladder cell line was not present in the animal bladders exposed to the typical bladder microenvironmental changes produced by dapagliflozin. (b) (4)

Most of the reviewers (and AC panel members) seem to be of the opinion that causality of dapagliflozin is difficult because of multiple confounding factors (nicely detailed in Dr. Mahoney's review). However, most also feel that the finding cannot be disregarded and deserves further study. The applicant has proposed several postmarketing safety measure including enhanced surveillance, pharmacoepidemiologic studies and blinded adjudication of bladder cancer events in their long-term CV outcome trial (CVOT). I believe that the large CVOT has the greatest opportunity to further define this signal.

Breast Cancer

There remains a numeric imbalance of breast cancer cases favoring the comparator arm (0.45% and 0.21% for dapagliflozin and comparator arms respectively IRR 2.472; 95% CI 0.636 to 14.095). This represents a decline in the IRR since the 2011 AC meeting (IRR was 4.41; 95% CI 0.57 to 200.86). Most, including consultants from the Division of Oncology

² This IRR includes the additional female patient that was captured after the integrated database lock. The IRR of the original database lock is 5.17 (95% CI, 0.677 to 233.55)

Products, believe this imbalance is probably a spurious finding. Reasons for this belief is lack of screening mammography prior to study entry and most diagnoses occurring relatively soon (i.e., less than one year) after randomization into the clinical trials. I agree with this assessment.

Cardiovascular Safety

As noted in my previous review, dapagliflozin does effect a mean decrease in blood pressure (≈ 3 mmHg systolic) and a mean decrease in weight ($\approx 1-5$ kg depending upon population studied). It is therefore not unreasonable to speculate that dapagliflozin use should be CV neutral or perhaps may even have cardiovascular benefit if the diuretic/blood pressure surrogate marker is transferable from existing anti-hypertensive medications that affect diuresis through a sodium excretion mechanism.

The original application compared a composite of time to first event for CV death, myocardial infarction (MI), stroke, and hospitalization for unstable angina in those taking dapagliflozin compared to all comparators. The meta-analysis comparing dapagliflozin to comparators (placebo and active control) demonstrated a hazard ratio (HR) of 0.67 (98% CI: 0.4-1.2-based on 78 events) and did not indicate any type of cardiovascular risk.

However, the sponsor submitted additional data to evaluate the potential cancer signal, including Trials 18 and 19. The additional data, when combined with what was already submitted, yielded a HR of 0.82 (CI: 0.58, 1.15-based on 145 events). Therefore, the additional data moved the HR more towards unity. This was summarized in the table below from Dr. Parks' original review (page 17).

Table 8.8. Primary Composite and MACE Analyses of Original MA and Updated MA

	Original Meta-analysis Stratified HR (98% CI)	Updated Meta-analysis Stratified HR (95% CI)
Primary composite of CV death, NFMI, stroke, and hospitalization for UA	0.67 (0.38, 1.18)	0.82 (0.58, 1.15)
MACE (CV death, NFMI, stroke)	0.60 (0.32, 1.10)	0.79 (0.54, 1.17)

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MA, meta-analysis; MACE, major adverse cardiovascular events; NFMI, nonfatal myocardial infarction; and UA, unstable angina.

The additional data contained two trials (Trials 18 and 19) that warrant independent evaluation. These two trials were of similar design and in similar populations, and were specifically design for cardiovascular outcome evaluation in high-risk groups, and therefore the results may be viewed as more reliant than an evaluation of the overall database.

Trials 18 and 19 did not mirror the overall result as their HR is greater than unity. In addition, if the traditional MACE definition is used, which allows only more objective endpoints, and perhaps less 'noise' that would bias the results toward unity, the following result was obtained (Dr. Parks' original review, page 19).

Summary of MACE using Cox Proportional Hazards Methods for Studies 18 and 19, combined.

	Dapagliflozin (a)	Comparator (b)
Number of Subjects With at Least One Events	24	19
Number of Subjects in Treatment Group	939	945
Total Subject-Years at Risk	708	709
Subjects with Events/1000 Subject-Year	33.88	26.80
Hazard Ratio Versus Comparator		
Estimate	1.266	
95% CI (c)	(0.693 , 2.311)	

Source: Table 25 from Sponsor’s Supplemental CV events Meta-analysis Report

The updated CV safety analyses with this submission included final results from Trials 18 and 19. The point estimate for the meta-analysis of strict MACE for these two trials decreased toward unity (HR 1.11; 95% CI, 0.67 to 1.83) and point estimate for MACE+³ was 0.98 (95% CI, 0.64, 1.49).

The overall meta-analysis (MACE+) included 97 events among 5936 subjects randomized to dapagliflozin and 81 primary events observed among 3403 subjects randomized to comparators in 21 trials and yielded an estimated hazard ratio of 0.81 (95% CI; 0.59, 1.09). The corresponding HR for MACE was based on 135 total events and was 0.78 (95% CI; 0.55, 1.11). The upper bound of the 95% confidence interval meets the risk margin of 1.8 necessary to demonstrate adequate pre-marketing CV safety in accordance with the FDA Diabetes Guidance of 2008⁴. Noted, as with canagliflozin, another SGLT2 inhibitor approved earlier this year, there is an imbalance in events during the first 30 days of exposure not favoring dapagliflozin. Exploratory analyses do not seem to identify a risk factor and the number of events is small limiting interpretability. This finding can be further explored with the large ongoing CVOT.

Advisory Committee Meeting

An AC meeting was held on December 12th. The AC meeting vote (approval: yes-13, no-1) with comments are detailed in the other clinical reviews. The majority of panel members believed that the issue of DILI had been resolved. There was a great deal of discussion regarding the imprecision of CV effect from the meta-analysis, but most agreed that the results met the criteria of the Diabetic CV evaluation guidance. Panel members struggled with the bladder cancer issue, and agreed it was important to collect further data post-marketing. There also was agreement that the signal was probably a chance finding, but further data could assuage lingering concerns.

³ CV death, MI, stroke, hospitalization for unstable angina

⁴ Guidance for Industry Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008

Conclusions and Recommendations

As I stated in my first review, dapagliflozin has demonstrated efficacy in controlling glycemic control in patients with T2DM that have normal or mild renal insufficiency and that efficacy has not been demonstrated in patients with moderate or severe renal insufficiency.

The issue that led to a CR action was the cumulative uncertainty regarding safety issues. Regarding the cumulative uncertainty, I agree with the AC panel members that the potential for dapagliflozin to contribute to DILI has been clarified with further data and is no longer an issue. I believe that further data has defined the potential CV effect to allow for marketing as well, pending results of the CVOT. I also believe that the breast CA finding was probably spurious.

This leaves us with the bladder cancer signal. As I expressed in my first review, it is always difficult to know what to conclude when confronted with a safety signal based on only a few events, particularly when there are not any preclinical concerns. For cancer safety signals, one can factor in the length of exposure prior to diagnosis and confidence interval surrounding the point estimate of the rate ratio in determining the likelihood that the signal may be real. Time of exposure is important as the position could be adopted that it may be difficult to consider a drug that does not have pre-clinical indicators as a carcinogen, to be a cancer inducer with the limited time exposure that is available in the NDA database. This consideration may be different however if the drug is a tumor promoting agent determined by appropriate preclinical testing. The magnitude of the rate ratio point estimate is important as the higher the ratio, the greater the magnitude of harm should it be a true finding and not random error and must be considered in any risk:benefit calculation.

At the time of the first action, I was sympathetic to those that feel most imbalances based on few events are spurious findings. It is difficult to conceptualize that exposure of less than a year to a drug that is not genotoxic or clastogenic would actually cause cancer in such a short time period. Additionally, we look at virtually hundreds of safety issues and categories and should expect (as was shown by the sponsor at the most recent AC meeting) that there will be imbalances in some of those evaluations, some favoring the drug and some not favoring the drug. Therefore, I do not find some imbalances, particularly those of limited magnitude, when considering limited numbers of events, concerning in and of themselves. The bigger concern occurs if the magnitude is several-fold greater and the public health impact should the finding not be by chance. However, it is easy to still be skeptical of findings that are of several-fold magnitude greater. I used the follow example from the RECORD trial⁵ as I felt it illustrated this concept.

⁵ Home PD, et. al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomized, open-label trial. *Lancet*. 2009 Jun 20;373(9681):2125-35.

As noted above for pancreatic cancer, there were 15 events which is similar to the number of events that we are considering in this application for breast and bladder cancer and the finding is similar, except it is favorable for rosiglitazone. Given the data above, one might conclude that those taking rosiglitazone experienced protection from developing pancreatic cancer. Yet, no one really believed that rosiglitazone was protective against pancreatic cancer and most felt this finding was spurious. Indeed, other trials did not repeat this finding.⁶ As such, one might wonder why we would consider the rosiglitazone finding above (when it is favorable) a chance finding, but would have greater reservations making the same conclusions for the unfavorable cancer imbalances in this application. Of course the reason is that a safety 'harm' issue warrants closer inspection as we should first 'do no harm'.

The bladder cancer issue is not fully resolved. The sponsors will evaluate the CV risk of dapagliflozin with a dedicated event-driven CVOT (D1693C00001-DECLARE-TIMI 58) with the goal of showing that the upper bound of the 95% confidence interval for the hazard ratio of MACE is smaller than 1.3 relative to placebo. This trial started in April 2013, will randomize up to 17,150 subjects (for 77,000 patient-years of exposure) to dapagliflozin 10 mg or placebo with a median expected follow-up time of 4.5 years and a total duration of six years. As part of this trial, bladder cancer evaluation will be performed. I believe this is the only way to put this issue to rest. The question becomes should this be performed before or after approval. I believe that there is enough uncertainty in this remaining issue (as opposed to when there were several open issues) that evaluation can be performed as part of a post-marketing requirement.

I recommend approval on this application with appropriate labeling.

⁶ One can only imagine what the scientific community would have felt had these numbers been reversed.

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/s/

CURTIS J ROSEBRAUGH
01/08/2014